REMARKS/ARGUMENTS

I. THE INVENTION

The present invention provides methods and articles for characterizing the interaction between components of a multicomponent biological complex and for detecting differences in the interaction of components between different samples. In particular, the specification states that:

> The methods involve capturing a multicomponent biological complex onto a solid support...through one of the components, particularly by using a biospecific affinity reagent. Then the complex is washed with a series of buffers of changing (e.g., increasing) stringency. The washes in the series form a gradient characterized by an increasing or decreasing concentration of a solute in the wash solution. The wash solutions are collected. Then the washes are examined to determine whether one of the components of the complex has been washed off in any of the wash solutions. (Emphasis added)

See, paragraph [0007] of the Pre-Grant Pub. No. 20040146937. As discussed herein, this is very different from the teaching of the prior art cited in the Office Action. In particular, Hutchens *et al.* employs a method of retentate chromatography, in which what is retained on the solid support, and not the washes, is examined. As discussed in more detail below, the present invention is novel and non-obvious over the prior art.

II. STATUS OF THE CLAIMS

With entry of this amendment, claims 1-35 are pending. Claims 1, 5, 21-23, 25, 26, 28-31, 33, and 34 are amended. Independent claims 1, 22, 28, and 31 are amended to clarify the step of immobilizing the multicomponent biological complex on to a solid support. Dependent claims 21, 25, 26, 29, 30, 33, and 34 are amended so be consistent with the independent claims from which they depend. Claim 5 is amended to remove "nucleic acid" from the Markush group, so that it is consistent with claim 1, from which it depends. The amendment to claim 23 merely clarifies that pairs are selected from the Markush group. No new matter is added with entry of this amendment.

III. CLAIM OBJECTION

The Examiner has objected to claim 5, alleging that it lacks a period at the end of the sentence.

Applicants have corrected the informality, and request that the Examiner withdraw the objection in light of claim 5 as presently recited.

IV. 35 U.S.C. 112 SECOND PARAGRAPH

Claim 5 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter the Applicant regards as the invention. Specifically, the Examiner points out that the Markush group recites that the affinity molecule can include a nucleic acid. However, claim 5 depends from claim 1, which excludes the affinity molecule from being a nucleic acid.

Applicants thank the Examiner for pointing out this inconsistency, and have amended claim 5 to remove nucleic acid from the Markush group. Applicants believe that claim 5 as amended sufficiently address the Examiner's concerns, and request that the rejection be withdrawn.

V. 35 U.S.C. 102(b)

Claims 1-6, 8-21, and 28-30 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hutchens *et al.*, U.S. Pat. No. 6,225,047.

Independent claims 1 and 28 are not anticipated by Hutchens *et al.*

The Examiner cites Hutchens *et al.* as disclosing an assay method utilizing an adsorbent comprising a polypeptide (*see*, col. 5, lines 21-22 of Hutchens *et al.*), contacting the adsorbent with a sample containing analytes, and detecting the retention of adsorbed analytes by desorption spectrometry such as SELDI (see, col. 18, lines 25-32 and col. 24, lines 46-49 of Hutchens *et al.*). The Examiner further alleges that Hutchens *et al.* teaches detecting material unretained on the adsorbent (*see*, col. 36, lines 63-67). Furthermore, the Examiner alleges that Hutchens *et al.* teaches the use of eluants (including various salts having increasing or decreasing concentrations), and a variety of analytes that may be resolved with the method, including

fragments of biological macromolecules, which are deemed by the Examiner to be the claimed first and second components of a multicomponent biological complex.. *See*, bottom of page 3 to the top of page 4, of the Office Action, *citing*, col. 32, lines 2-11 and col. 34, lines 9-15, of Hutchens *et al.* Applicants traverse the rejection to the extent that it applies to the claims as presently amended.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628,631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited reference must contain every element of the claims at issue. The cited reference, Hutchens *et al.*, does not.

First, Applicants note that Hutchens *et al.* teaches a method of retentate chromatography, in which the component retained on the adsorbent is detected. This is very different form the present invention as claimed in independent claims 1 and 28, where it is the eluted component that is detected. Hutchens *et al.* does not teach or suggest detecting the eluted component as claimed in the present invention.

With regard to the Examiner's allegation that Hutchens *et al.* teaches detecting materials that are unretained on the adsorbent (*see*, page 3, of the Office Action, *citing* col. 36, lines 63-67, of Hutchens *et al.*) Applicants disagree with the Examiner's interpretation. Specifically, the passage referred to by the Examiner states that:

> In another embodiment unretained sample is, itself, analyzed for analytes by any analytical technique. Even after a single retention step, this process allows one to examine materials adsorbed to an adsorbent and those analytes that are not adsorbed.

This is clearly very different from the presently claimed method. For example, independent claims 1 and 28 require:

> ...immobilizing the multicomponent biological complex on a solid support through a biospecific affinity molecule...washing the immobilized multicomponent biological complex...and...measuring for a second component in each of the elution washes....

Nowhere does Hutchens *et al.* teach that the analyte is first retained by the absorbent, then washing the analyte retained by the adsorbent and then measuring the wash for

presence of an analyte released from the adsorbent. Rather, in the embodiment referred to by the Examiner, Hutchens *et al.* teaches detecting material that was not retained by the absorbent. This is very different from the present invention, where the analyte must first be bound (adsorbed) to the solid support, and then eluted.

Contrary to the Examiner's assertion, Hutchens *et al.* does not teach or suggest immobilizing a multicomponent biological complex on a solid support through a biospecific affinity molecule, washing the immobilized complex with a sequence of elution washes, and measuring for a second component in each of the elution washes, as recited in independent claims 1 and 28. Therefore, Hutchens *et al.* does not anticipate independent claims 1 and 28 as presently recited.

In view of the above, Hutchens *et al.* does not anticipate independent claims 1 and 28, because Hutchens *et al.* does not disclose all of the salient elements as presently recited in claims 1 and 28. Applicants therefore respectfully request that the Examiner withdraw the rejection.

Claims 2-6, and 8-21 depend either directly or indirectly from claim 1 and include all of the limitations of independent claim 1. Similarly, claims 29 and 30 depend from independent claim 28, and include all of the limitations of independent claim 28. Therefore, the arguments presented above with regard to independent claims 1 and 28 are also applicable to the rejected dependent claims.

In view of the above, Applicants respectfully request that the Examiner withdraw the rejection.

VI. 35 U.S.C. 103(a)

A. Burden of Proof in Establishing *Prima Facie* Obviousness

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the Examiner fail to establish

a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained in more detail below, the Examiner has not established a proper *prima facie* case of obviousness because the cited references do not, expressly or impliedly, teach or suggest all of the elements of the invention as presently claimed.

B. Claims 22, 23, 25-27, and 31-35 are not obvious under 35 U.S.C. §103(a) in view of Hutchens *et al* (U.S. Pat. No. 6,225,047).

Claims 22, 23, 25-27 and 31-35 are rejected under 35 USC 103(a) as being unpatentable over Hutchens *et al.*, U.S. Pat. No. 6, 225,047. Independent claims 22 and 31 relate to providing sets of biological samples, where each subset is characterized by a different biological characteristic. In addition to the alleged teaching of Hutchens *et al.* cited above, the Examiner also cites Hutchens *et al.* as allegedly teaching performing the same assays on samples from normal human patients and cancer patients to allow for identification of potential disease markers, and that varying the elution characteristics allows for detecting many different types of analytes. *See*, bottom of page 5, to top of page 6, of the Office Action, *citing*, col 65, lines 31-45 and col 37, lines 10-14, of Hutchens *et al.* The Examiner acknowledges, however, that the examples relating to the assays from normal human patients and cancer patients disclosed in Hutchens *et al.* do not appear to use different elution characteristics. *See*, page 6, of the Office Action, *citing*, col. 32, lines 2-11, of Hutchens *et al.* Moreover, with regard to claim 27, the Examiner cites Hutchens *et al* as using a computerized learning algorithm to classify a profile. Applicants traverse the rejection on the grounds that the Examiner has not established a proper *prima facie* case, as discussed in more detail below.

Even if Hutchens *et al.* did teach the use of different elution characteristics, which the Applicants contest, or the use of a computerized algorithm to classify a profile, Hutchens *et*

al. would still not render the rejected claims obvious. Specifically, claims 23 and 25-27 depend from independent claim 22, and therefore include all of the limitations of independent claim 22 as presently recited. Claims 32-35 depend either directly or indirectly from independent claim 31, and therefore include all of the limitations of independent claim 31 as presently recited. Both independent claims 22 and 31 include the same limitations as independent claims 1 and 28 discussed above with regard to the 102(b) rejection, namely that that the "...multicomponent biological complex from the sample [be] immobilized on a solid support through a biospecific affinity molecule...washing the immobilized multicomponent biological complex...and... measuring for a second component in each of the elution washes...." For the same reasons as discussed *supra* with regard to independent claims 1 and 28, Hutchens *et al.* does not teach or suggest all of the salient elements of independent claims 22 and 31. Because Hutchens *et al.* does not teach or suggest immobilizing a multicomponent biological complex on a solid support through a biospecific affinity molecule, washing the immobilized complex with a sequence of elution washes, and measuring for a second component in each of the elution washes as recited in independent claims 22 and 31, the rejected independent claims are not obvious in view of Hutchens *et al.*

C. Claim 24 is not obvious under 35 U.S.C. §103(a) in view of Hutchens *et al.*, (U.S. Pat No. 6, 225,047) and Morin *et al.*, (U.S. Pat. No. 6,599,728).

The Examiner cites Hutchens *et al.*, for the reasons stated *supra*. The Examiner, acknowledges that Hutchens *et al.*, does not teach an embodiment where one sample is exposed to an inhibitor RNA, while another sample is not exposed to the inhibitor RNA, as recited in claim 24. *See*, top of page 7 of the Office Action.

The Examiner, however, cites Morin *et al.* (U.S. Pat No. 6,599,728) as teaching the introduction of inhibitory RNA to modulate Tankyrase II expression in a cell (col. 3, lines 37-43 of Morin et al) and that compounds that modulate Tankyrase II can be used to screen random combinatorial libraries of small molecule compounds or as a part of rational drug design, and the use of positive and negative controls. *See*, col. 20, lines 9-15 and col. 16, lines 47-50, of Morin *et al.*

Applicants contend that the Examiner has not established a proper *prima facie* case of obviousness, because Hutchens *et al.*, in view of Morin *et al.*, does not teach all of the

elements of claim 24. Specifically, claim 24, depends from claim 22 and therefore includes all of the limitations of claim 22. As discussed *supra*, Hutchens *et al.*, does not teach or suggest immobilizing a multicomponent biological complex on a solid support through a biospecific affinity molecule, washing the immobilized complex with a sequence of elution washes, and measuring for a second component in each of the elution washes as recited in independent claim 22, and Morin *et al.*, does not cure this defect. Because Morin *et al.* does not cure this defect, claim 24 is not obvious in view of the cited references.

In light of the above, the Applicants respectfully request that the Examiner withdraw the rejection.

D. Claim 7 is not obvious under 35 U.S.C. §103(a) in view of Hutchens *et al.*, (U.S. Pat No. 6, 225,047) and Beutler *et al.* (U.S. Pat. No. 5,234,811).

The Examiner cites Hutchens *et al.* for the reasons stated *supra*. The Examiner acknowledges, however, that Hutchens *et al.* does not teach an embodiment where the nucleic acid is bound to the solid support after binding the multicomponent biological complex, as recited in claim 7.

The Examiner, however, cites Beutler *et al.*, as teaching that the probe/target hybrids may be selectively isolated on a solid matrix, as an alternative to immobilizing the probe nucleic acids on a solid support and using it to capture the target sequences from the solution. The Examiner alleges that it would have been obvious to one of skill in the art to allow binding of the double-stranded nucleic acid molecules to its target in Hutchens *et al.*, before immobilizing the probe target hybrids to the solid support because Beutler *et al.*, teaches that probe/target hybrids may be selectively isolated on a solid matrix.

Applicants contend that the Examiner has not established a proper *prima facie* case of obviousness, because Hutchens *et al.*, in view of Beutler *et al.*, does not teach all of the elements of claim 7. Specifically, claim 7, depends from claim 1 and therefore includes all of the limitations of claim 1. As discussed *supra*, Hutchens *et al.*, does not teach or suggest immobilizing a multicomponent biological complex on a solid support through a biospecific affinity molecule, washing the immobilized complex with a sequence of elution washes, and measuring for a second component in each of the elution washes, and Beutler *et al.*, does not cure this defect.

In light of the above, the Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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